substituted variant thereof." Thus claims 2 and 11 and claims dependent thereon particularly point out and distinctly claim the subject matter of the invention.

Claim 10 is rejected as being indefinite as lacking in a step necessary to carry out the claimed function. Claim 10 has been amended to recite the element "at least one adenoviral vector is introduced into the neoplastic cell", which was recommended by the Examiner in paper number 16 and which provides the necessary step of getting the adenoviral vector into the cell in order to have the claimed effect. Thus claim 10 and claims dependent thereon particularly point out and distinctly claim the subject matter of the invention. Applicants request that the rejection of claims 1-5, 10-15, 20-22 and 24 be withdrawn and the claims allowed.

Rejections under 35 U.S.C. Section 112, first paragraph.

Claim 1-5, 10-15, 20-22 and 24 stand rejected as not being described in the specification in a way that enables the skilled artisan to make and/or use the invention. The Examiner contends that the claimed invention must be limited only to those preferred embodiments that are specifically exemplified in the specification. However, according to patent law and practice, the claimed invention is not limited by the disclosure of the specification. See *SRI International v. Matsushita Elec. Corp.*, 775 F.2d 1107, 227 USPQ 577 (Fed. Cir. 1985) (*in banc*). Furthermore, the embodiments that are described in the specification are "just [preferred embodiments], and the scope of a patentee's claims is not necessarily or automatically limited to the preferred embodiment[s]." *Amhil Enterprises Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 38 USPQ2d 1471 (Fed. Cir. 1996).

The Examiner also asserts that "the specification fails to provide any theoretical basis for the claimed adenoviral recombinants to replicate better in neoplastic cells that are dividing as compared to neoplastic cells that are non-dividing (e.g. cells in G_0 phase)". According to the patent statute and case law, no theoretical basis is required to support the invention, in fact even working examples are not required, merely that the invention is described and that the skilled artisan has a reasonable expectation of success in practicing the invention. See MPEP Sections 2164.08(b) and 2165.01, and *In re Gay*, 309 F.2d 768, 135 USPQ 311 (CCPA 1962). Applicants respectfully point out that all skilled oncologists understand that neoplastic cells are by definition *not quiescent* (i.e., neoplastic cells are not in G_0) but are in a state of unregulated cell division and mitosis. Cancers are only threatening when they are growing, and growth is associated with cell proliferation, which is the opposite of quiescence. The third edition of Albert's *et al.*, states on page 1256, "Cancer cells are defined by two heritable properties: they and their progeny (1) reproduce in defiance of the normal restraints [which means that the cells are committed to divide and thus can not be quiescent] and (2) invade and colonize territories normally reserved for other cells. ... An isolated abnormal cell that does not proliferate more than its normal neighbors does no

significant damage, no matter what other disagreeable properties it may have; but if its proliferation is out of control, it will give rise to a tumor, or *neoplasm*-- a relentlessly growing mass of abnormal cells." Hence, to treat neoplasms, there is no need to target G_0 cells.

Applicants also point out that representative embodiments of the claimed invention have been used to successfully in the treatment of *human* tumors in an art recognized nude mouse model, thus demonstrating the effectiveness and utility of the invention. See Examples 4, 5 and 8 of the instant specification, especially Example 8, which demonstrates the effectiveness of both the KD1-related vectors and the GZ1-related vectors in treating human tumors *in vivo*.

The Examiner also points out that that the "use of cytolytic vectors in tumor cell 'purging' procedures is a relatively undeveloped art, not routinely used with any predicatable level of efficacy..." Applicants remind the Examiner that "The Federal Circuit has reiterated that therapeutic utility [i.e., efficacy] sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs marketed in the United States," MPEP Section 2107.01. See also *Cross v. Iizuka,* 753 F.2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985), which discusses the requirements for sufficient *in vitro* or *in vivo* testing of a patentable therapeutic composition.

Nonetheless, claims 1, 10 and claims dependent thereon have been amended to be drawn to *adenovirus vectors* as opposed to any and all vectors. This amendment narrows the scope of the invention to those types of vectors that are most fully described in the specification and exemplified in the working examples. Thus, the claims comply with 35 U.S.C. Section 112, first paragraph and are patentable under the law.

Claim 2 (and 11 in part) remains rejected as being overly broad in its recitation of conservatively substituted variants of disclosed ADP sequences. Claims 2 and 11 have been amended to be drawn to specific sequence identifiers, and therefore can no longer be held to be overly broad on the basis of non-enablement. Claims 2 and 11 thus comply with 35 U.S.C. Section 112, first paragraph and are patentable under the law.

Method claims 10-15, 20-24 are rejected as being non-enabling for *in vivo* applications. Applicants remind the Examiner that the Examples of the specification, especially Examples 4, 5 and 8, demonstrate that the claimed anticancer adenoviral vectors do in fact work *in vivo*. There is no requirement under the law that efficacy of the vectors be demonstrated in human experiments (see again MPEP Section 2107.01). Furthermore, Little et al., (U.S. Patent No. 6,254,862) and Henderson et al., (U.S. Patent No. 6,197,293) describe and claim (claim 20 of '293 and claim 37 of '862) adenoviral vectors that inherently overexpress ADP to be used as *in vivo* anticancer vectors. In view of the '293 and '862 patents, which is presumed to be valid under patent law and thus must contain a disclosure sufficient to enable the skilled artisan to *administer* an effective does of the anticancer vector to a tumor, the skilled

artisan would readily expect that the anticancer adenoviral vectors claimed in the present invention would be effective as an antitumor treatment method. Applicant asserts that claim 10 and other methods of treatment claims are thus enabled.

Regarding the rejection of claim 14 (which recites a passive immunization step) as lacking in enablement because the *in vivo* nude mouse model lacks an immune system, Applicant respectfully reminds the Examiner that while an athymic mouse lacks the ability to elicit an immune response *de novo*, since it lacks functioning helper T-cells, nonetheless still comprises a fully functional complement system that is able to facilitate antibody-mediated cytolysis. Recall that the complement system exists independently of a functioning immune system and interacts with antibodies to cause cell-lysis (see generally Abbas et al., pp. 294-299). Applicants also present the abstract of a paper by Takahashi et al (1995), which demonstrates the efficacy of antibodies administered to a nude mouse to effect tumor cell killing via NK cell or macrophage mechanism. Thus, passive immunity can function in nude mice through a variety of mechanisms unrelated to T-cell activity and the skilled artisan would thus have reasonable expectation of success in employing the method of claim 14.

Regarding claim 24, the Examiner contends that the Applicant has failed to "address any *theoretical* advantage to using replication-defective adenovirus in the context of the claim which already has a replication-competent virus present." In Applicants' response to the previous office action of paper number 13, Applicants pointed out that the replication-competent vector provide complementary gene activity to allow replication, and thus *expansion and spread* of the replication-defective viruses throughout the neoplastic cells (see again Example 5, which shows the expansion of a replication-defective vector through a neoplasm when administered in conjunction with the KD1 or KD3 vector). An important point is that the replication-defective vectors *can be administered at much lower doses* since they can replicate when complemented by the replication-competent vectors of the present invention. Thus any and all replication-defective vectors that deliver anticancer compounds can be used in conjunction with the KD1-like vectors that deliver ADP to neoplastic cells. Quite simply, the specification clearly teaches the *enhanced killing effect* of the anticancer adenoviral vectors of the instant invention with a myriad of current anticancer therapies, including chemotherapy (viral-based or chemical) and radiation therapy. While the Examiner may not accept the theoretical underpinnings of how an adenovirus vector that is replication-competent in neoplasm can facilitate the replication and spread of a non-replication competent vector throughout the neoplasm or believe that such an approach has utility, the fact remains that Example 5 shows the *improved* spread of said non-replication competent vector through a *bona fide* human tumor (page 31, paragraph 1). Regarding the utility issue, it may help the Examiner to think about using the replication-competent vectors of the present invention in conjunction with currently available replication-defective vectors. For example, why continue to redesign and rebuild

the replication-competent vector to accommodate other anticancer encoding genes, when the currently available vectors comprising said anticancer encoding genes can be simply administered with the present anticancer vector? Applicants would argue that this is sufficiently useful and novel application.

Examiner also contends in his rejection of the claims based upon the vascular permeability issue, that the working examples, which demonstrate *in vivo* the effectiveness of various embodiments of the instant invention, can not be extrapolated to other types of tumors that have not been shown in the examples. Examiner also restates his view that the Fox article underscores the unpredictability of administering a replication-competent vector to neoplasms. Applicants remind the Examiner that the scope of the claims are not to be limited to the disclosed embodiments of the specification, but rather are to be limited in scope by the language of the claim. In every tumor example and neoplastic cell culture example provided, the vectors of the claimed invention were effective in slowing or reversing the growth of neoplasms *in vivo* or in killing neoplastic cells *in vitro*. The Examiner however continues to argue the relevance of the working examples to *in vivo* treatment claims. Again the Examiner is reminded that the requirements for patentability and FDA clinical acceptance of a new therapy require very different criteria. See again MPEP Section 2107.01. See again *SRI International v. Matsushita Elec. Corp.*, 7775 F.2d 1107, 227 USPQ 577 (Fed. Cir. 1985). Applicants assert that the specification provides sufficient evidence of operability of the claimed invention.

Regarding the unpredictability issue as presented in the Fox commentary, Applicants assert that the athymic (nude) mouse model demonstrates the effectiveness of this invention in the treatment of human neoplasms. For example, Henderson et al. (Patent '293) demonstrate the effectiveness of their replication-competent anticancer vector via athymic mouse models (column 47, lines 19-43). Applicants thus assert that the invention is enabled by the specification and therefore complies with 35 U.S.C. Section 112, first paragraph and request that the rejection be withdrawn and the claims allowed.

Rejection under 35 U.S.C. Section 102(e).

Claims 1-4 and 10-13 remain rejected as being anticipated by Henderson (patent no. 6,197,293) or Little (patent no. 6,254,862). Both of these references disclose a recombinant adenoviral vector which is replication-restricted to neoplastic cells and which overexpresses an adenovirus death protein. Both of these patents have priority dates of March 3, 1997 and are cited as teaching the same thing (that same thing being the CN751 vector), therefore Applicants will address both of these documents together for the sake of clarity and convenience.

Applicants herein present the declaration of Dr. William Wold under 37 C.F.R. 1.131, along with exhibits A-E, which demonstrate the conception of the invention and diligence toward reduction to practice of the instant invention before the priority date of the '293 and '862 patents. The instant invention

as claimed is an adenoviral vector capable of replicating in neoplastic cells and overexpressing ADP. Before presenting our case, Applicants remind the Examiner that "[c]onception of a species within a genus may constitute conception of the genus" and that "reduction to practice of species establish[es] priority to genus." *Oka v. Youssefyeh,* 849.F.2d 581, 7 USPQ2d 1169 (Fed. Cir. 1988) and *Mikus v. Wachtel,* 504 F.2d 1150, 1151, 183 USPQ 752, 753 (CCPA 1974).

According to the sworn declaration of Dr. Wold, the principal investigator on the anticancer vector project and a co-inventor of the instant invention, the conception in the mind of the inventor of the instant inventor occurred before July 20, 1994. As evidence in support of this assertion, Applicants present the abandoned patent application 08/277,737, filed July 20, 1994 ("Exhibit A"), which describes a vector that inherently overexpresses ADP and is replication competent and may be used therapeutically to remove cells. (See Exhibit A, page 23, line 25 and page 24, lines 2-9.) Applicants also present a proposal sent by Dr. Wold to Dr. Burke of Chiron Corporation on July 27, 1994 ("Exhibit B") that describes adenoviral vectors that are nondefective for replication, inherently overexpress ADP, and utilize ADP as a tumor cell-killing therapeutic. (See Exhibit B, page 3, lines 4-7, page 4, line 16 - page 5, line 9 and page 8, line 13.)

Diligence toward reduction to practice began on July 13, 1996 (see declaration of Dr. Wold, page 4, first sentence under the heading "Antitumor vector building) with the generation of high titre *dl*1101/1107 stocks, and continued through the filing of the instant application on July 12, 1999. The KD1 species was produced or actually reduced to practice on February 20, 1997 (declaration of Dr. Wold, page 5, last line of first paragraph.) Initial *in vivo* tumor tests demonstrating effectiveness of the instant anticancer vectors were concluded on April 21, 1999 (see Diagnostic Laboratory Health Evaluation dated October 29, 1999 ["Exhibit E"] from the Department of Comparative Medicine at Saint Louis University).

To support the declaration of Dr. Wold, Exhibits C through E are presented to corroborate the dates on which various experiments were performed in the diligent reduction to practice of the instant invention. The Certificate of Analysis from GIBCO BRL, dated 09/26/96 ("Exhibit C") is presented as evidence of the procurement of oligonucleotide KD6, which was used in the construction of GZ1 and KD1 vectors. The facsimile from Dr. Whitsett with the date stamp of 01/09/98 ("Exhibit D"), which reports on the effectiveness of the KD1 and KD3 vectors in reducing tumors, is presented as evidence of timely *in vivo* nude mouse studies, which were necessary to prove the effectiveness of the instant invention as an anticancer therapeutic vector. Exhibit E, which clearly depicts the 4/21/99 date of necropsy of test animals, is presented as evidence of *in vivo* tests to determine the effectiveness of the instant anticancer vectors toward a completely different type of tumor (HEP 3B tumors) than those tested by Dr. Whitsett (A549 tumors), which experiments were necessary to establish the broad therapeutic applicability of the instant anticancer vectors.

In conclusion, Applicants declare that the diligent reduction to practice of the instant invention was begun on July 13, 1996, which preceded the March 3, 1997 date of priority of the '862 and '293 patents. Therefore, given the priority of Applicants' invention to July 13, 1996, the '862 and '293 patents can not anticipate the claims of the instant invention under 35 U.S.C. Section 102(e). Applicants respectfully request that the rejection of claims 1-4 and 10-13 under 35 U.S.C. Section 102(e) be withdrawn and the claims allowed.

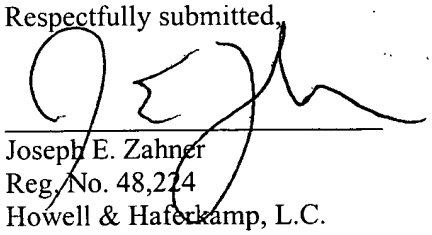
Rejection of claims under 35 U.S.C. Section 103(a)

Claims 1-4, 10-13 and 20-22 remain rejected as being obvious over the Henderson patent (6,197,293) or the Little patent (6,254,862), both in view of Freytag et al. Freytag et al. teaches multiple modalities of tumor cell killing. The 131 declaration submitted herein establishes the date of diligent reduction to practice of the instant invention as July 13, 1996, which is prior to the priority date of March 3, 1997 of the '862 and '293 patents. Hence, the Henderson et al. and Little et al. documents, which must be removed as 102(e) references, can not be cited as prior art references in a 103(a) rejection. Applicants request that the rejection of the claims under 35 U.S.C. Section 103(a) be withdrawn and the claims allowed.

Conclusion

In view of the amendments made herein to the claims, and the arguments, evidence, declaration and exhibits put forth, Applicants believe that the claims are in a condition for allowance. Applicants respectfully request that all of the rejections to claims 1-5, 10-15, 20-22 and 24 be withdrawn and the claims allowed. If there are any other issues remaining, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



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AMENDED CLAIMS

1. (Twice Amended) A recombinant adenovirus vector which is replication-competent in neoplastic cells and which overexpresses an adenovirus death protein.

2. (Twice Amended) The adenovirus vector of claim 1 wherein the adenovirus death protein comprises SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, [or] SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12.

4. (Amended) The recombinant adenovirus vector of claim 2, wherein the recombinant adenovirus lacks expression of at least one E3 protein selected from the group consisting of: gp19K; RIDα; RIDβ and 14.7K.

5. (Twice Amended) The recombinant adenovirus vector of claim 4, wherein the recombinant adenovirus comprises SEQ ID NO:1 or SEQ ID NO:2.

10. (Twice Amended) A method for promoting death of a neoplastic cell comprising contacting the neoplastic cell with an adenovirus vector, wherein

(a) at least one adenoviral vector is introduced into the neoplastic cell, and

(b) said adenovirus vector is replication-competent in neoplastic cells and overexpresses an adenovirus death protein.

11. (Amended) The method of claim 10 wherein the adenovirus death protein comprises SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, [or] SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12.

12. (Amended) The method of claim 11, wherein the adenovirus vector comprises a recombinant adenovirus lacking expression of at least one E3 protein selected from the group consisting of: gp19K; RIDα; RIDβ and 14.7K.

13. (Twice Amended) The method of claim 12, wherein the neoplastic cell is contained in a tumor in a patient and the contacting step comprises administering the adenovirus vector to neoplastic cells of the tumor.

C4

15. (Amended) The method of claim 14, wherein the recombinant adenovirus comprises SEQ ID NO:1 or SEQ ID NO:2.

C5

24. (Amended) The method of claim 13, further comprising administering to the tumor one or more replication-defective adenoviruses, wherein each replication-defective adenovirus expresses an anti-cancer gene product, and wherein the recombinant adenovirus facilitates the spread of the replication-defective adenovirus in the tumor.

C6

28. (New) A recombinant adenovirus vector, wherein said adenovirus vector (a) is replication-restricted to dividing cells, (b) contains a mutation in the E1A gene, and (c) overexpresses an adenovirus death protein.